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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,506	11/09/2000	Arno Hartmann	MERCK-2056	2626

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	14

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,506	HARTMANN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *7-9,15,19 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10-14,16-18,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1-25* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed 09 November 2000 (Paper No. 4) has been entered in full.

The amendment filed 15 February 2001 (Paper No. 5) has been entered in full.

The amendment filed 12 March 2001 (Paper No. 6) has been entered in full.

The amendment filed 18 December 2002 (Paper No. 13) has been entered in full.

Applicant's election with traverse of Group I (claims 1a fusion protein, 2-14, 16-18, 24 and 25) in Paper No. 8 is acknowledged. The reasons for Applicant's traversal and the Examiner's response were made of record in the Restriction/Election filed 28 August 2002 (Paper No. 11).

Applicant's species election with traverse of Fc-EPOm (claim 1), Pro90→Ala (claim 6), C-terminal truncation with the amino acid position at 108 (claim 7), a fusion protein where position 33 is not Cys (claim 12) and a fusion protein with a Pro90→Ala mutation (claim 14) in Paper No. 11 is acknowledged. The traversal is on the grounds that a search and examination of the full scope of the claims would not impose a serious burden and that the restriction/election made by the Examiner would result in Applicants filing numerous applications to obtain patent protection for the claimed invention.

Applicant's arguments have been considered but not deemed persuasive. A search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter.

The instant claims encompass different species and requires an extensive search. Although the classifications for these various EPO proteins are overlapping, for

instance 530/350, each represents a patentably distinct product with distinct physical and functional characteristics and various mutations. Further the search for more than one product would be burdensome, because each search for a portion of a disclosed EPO amino acid sequence variant requires a separate "word search" of the amino acid databases. Lastly, while the added cost to the Applicants to file divisional applications is truly regretted, it is beyond the resources of the USPTO to permit examination of multiple inventions in a single application.

The requirement is still deemed proper and is therefore made FINAL. Claims 7-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Claims 1a, 2-6, 10-14, 16-18, 24 and 25 are under examination.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application. The specification refers to sequences on page 37, line 15 but does not identify the sequences by their sequence identifiers. Appropriate correction is required.

Applicant must submit a response to this Office Action and compliance with sequence rules simultaneously.

Claim Objections

Claims 1, 6, 10, 12, 13, 14, 17 and 18 are objected to because of the following informalities:

Claims 1, 6, 10, 12, 13, 14, 17 and 18 encompass non-elected inventions and/or species and require amendment to limit to elected invention. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation, "an erythropoietin (EPO) form having improved properties". The metes and bounds of the instant claim cannot be determined because an improved property is an ambiguous term.

Claim 5 depends on a claim drawn to a non-elected group. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 16 is indefinite in the recitation of "a fusion protein according to claim 1, said fusion protein being a whole Ig molecule". It is unclear how the entire fusion protein is a whole Ig molecule.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6, 16, 17, 18, 24, 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Sytkowski *et al.*, WO 99/02709.

Sytkowski teaches the production and use of erythropoietin/immunoglobulin fusion proteins with increased biological activity (page 5, lines 5-10). The instant claims allow for an unlimited number of mutations in erythropoietin and Sytkowski teaches erythropoietin analogs, variants, mutants and derivatives (claim 6) (page 5, lines 11-15 and page 8, line 17-page 12, line 22). Sytkowski teaches DNA encoding erythropoietin (EPO) fused at its N-terminus or C-terminus to DNA encoding an immunoglobulin constant region (page 3, lines 6-31 and page 16, lines 31-33). Sytkowski teaches that fusion proteins comprising erythropoietin and immunoglobulin polypeptide chains will

have increased biological activity and increased *in vivo* half-life relative to wild type (page 2, lines 10-30 and page 19, line 8-page 21, line 8). The immunoglobulin polypeptide chains of the invention can comprise either the heavy chain constant region or both the heavy and light chain constant region. The Fc portion of the immunoglobulin is defined as the immunoglobulin C-terminal domain that is produced upon papain digestion (column 14, lines 21-32) (claims 1, 2, 3, 6). The entire immunoglobulin heavy chain constant region can be fused to the erythropoietin molecule (claim 16) (page 15, lines 14-15). Sytkowski teaches the use of human Fc (page 23, line 20) and murine EPO (page 25, line 22) (claims 17, 18).

DNA encoding glycosylated or non-glycosylated EPO can be fused to the DNA encoding the immunoglobulin constant region (page 4, lines 4-11). DNA encoding EPO mutated to increase biological activity, can be fused to the immunoglobulin constant region (claim 5) (page 4, lines 12-18). The increase in circulating *in vivo* half-life can be extended from minutes to hours or days with the fusion protein (claim 4) (page 19, lines 14-24). Sytkowski teaches pharmaceutical compositions comprising the fusion protein and pharmaceutically acceptable carriers (claims 24, 25) (page 21, lines 9-31).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-13, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski *et al.*, WO 99/02709 in view of Okasinski *et al.*, US Patent No. 5,888,772. The teachings of Sytkowski et al. WO 99/02709 are described above in the 102(a) rejection. Sytkowski does not teach engineered cysteine residues.

Okasinski teaches the substitution of cysteine for arginine at position 139 of human erythropoietin (claim 10). Okasinski teaches human erythropoietin wherein cysteine at position 33 is replaced with another amino acid which results in improved *in vivo* activity (claim 12) (column 5, lines 1-9; column 6, lines 19-27; column 18, lines 64-67 and column 21, lines 43-46). Okasinski teaches EPO proteins which have a pattern of disulfide bonding distinct from human or mammalian erythropoietin and wherein the new engineered cysteine residues form a disulfide bond (column 24, lines 17-55 and Figure 4) (claim 13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the instant invention of a fusion protein of EPO and the

Fc portion of an immunoglobulin molecule wherein EPO has engineered cysteine residues. The motivation and expected success is provided by Sytkowski who demonstrates increased biological activity when EPO is fused with an immunoglobulin molecule and Okasinski who provides another means of increasing EPO activity by mutating cysteine residues.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
March 21, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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